British Heart Journal, 1978, **40**, 802-805

Heart type creatine kinase isoenzyme (CK MB) in acute cerebral disorders

MARKKU KASTE, HANNU SOMER[1], AND AARNE KONTTINEN

From the Department of Neurology, University of Helsinki, SF-00290 Helsinki 29; The Wihuri Research Institute, Kalliolinnantie 4 B, SF-00140 Helsinki 14; and Kivelä Hospital, SF-00260 Helsinki 26, Finland

SUMMARY Heart type creatine kinase isoenzyme (CK MB) was detected in the serum in 23 out of 53 patients (43%) with acute cerebrovascular, traumatic, or infectious brain damage. Electrocardiogram disclosed abnormalities suggestive of acute myocardial injury in 15 of these 23 patients. Eleven of them also showed increased LD_1 activity. Subendocardial haemorrhage was detected in 3 out of 8 necropsied patients with serum CK MB activity. Among those 30 patients in whom no CK MB activity was found electrocardiographic abnormalities suggestive of acute myocardial injury were observed in 2 and increased LD_1 was seen in 4 cases.

The mortality was higher if either CK MB isoenzyme or electrocardiographic abnormalities suggestive of acute myocardial injury were present, compared with the patients lacking these signs ($P < 0.01$).

Present findings suggest that acute brain damage may secondarily cause myocardial damage more often than has been believed before. Results also indicate that a combination of acute brain damage and acute myocardial injury often indicated a poor prognosis.

Several studies suggest myocardial involvement in acute cerebral disorders. Various electrocardiographic abnormalities have been described, but signs suggestive of ischaemic myocardial injury are few (see reviews Weidler, 1974; Weintraub and McHenry, 1974).

The lack of specificity of serum enzyme tests in confirming the myocardial damage has so far been a deterrent. Recent improvements in determination of heart type creatine kinase isoenzyme (CK MB) have made it possible to disclose myocardial damage (Roe *et al.*, 1972; Somer and Konttinen, 1972).

In a preliminary study concerning the release of brain type creatine kinase isoenzyme from brain to blood in acute cerebral disorders (Somer *et al.*, 1975) we also found CK MB isoenzyme in the serum of many such patients. We, therefore, decided to study how often it can be found in various acute cerebral disorders, and whether its presence would have any prognostic significance.

[1]Present address: Department of Neurology, College of Physicians and Surgeons of Colombia University, New York, N.Y. 10032, U.S.A.

Received for publication 13 June 1977

Patients and methods

We studied 53 patients (38 men and 15 women) with acute brain damage, between 18 and 82 years (mean 46·5 years). The diagnosis was ischaemic brain infarction in 27 cases, cerebral contusion in 10, subarachnoid haemorrhage in 8, cerebral haemorrhage in 4, bacterial meningitis in 4 cases, based on traditional clinical, laboratory, and radiological examinations. The patients showed signs of severe brain damage on admission, except those with ischaemic brain infarction. All patients were admitted for acute brain disease, not for cardiac symptoms.

Blood samples were collected on admission and daily during the first 3 hospital days, but a rigid time schedule could not always be achieved. All patients came to the hospital within 48 hours of the onset of symptoms, with the exception of 1 patient with ischaemic brain infarction and the patients with bacterial meningitis. The time from onset of symptoms to collection of first blood sample averaged 16·0 hours (SE 2·09 hours) in all but the subgroup with bacterial meningitis. In this latter group the estimation of onset was unreliable.

Total creatine kinase (CK) activity was measured

by using test kits (CK activated, Boehringer, Mannheim) at 25°C. The normal upper limit is 50 U/l. Creatine kinase isoenzymes were separated electrophoretically in agarose gel and determined by a fluorescence technique (Somer and Konttinen, 1972).[1] The method does not allow detection of serum CK MB activities lower than 3 U/l.

Lactate dehydrogenase (LD) and its isoenzymes were analysed in all but 2 cases with subarachnoid haemorrhage. The upper normal limit of total LD was 204 U/l and that of LD_1 was 101 U/l, with confidence limit $P < 0{\cdot}01$ (Konttinen *et al.*, 1969). An electrocardiogram was recorded twice daily during the first 3 hospital days in the case of patients with ischaemic brain infarction. In the other subgroups the electrocardiogram was not taken as systematically, and 4 patients with acute brain injury had no electrocardiogram. Necropsy was performed on 11 of 21 deceased patients.

The specificity of heart type creatine kinase isoenzyme for cardiac damage is shown in Table 1.

Student's t test and the χ^2 test were applied in statistical comparisons.

Table 1 *Incidence of heart type creatine kinase isoenzyme (CK MB) found in serum in various diseases and conditions*

	Cases with increased serum CK MB activity
Healthy controls	0/105
Athletes after muscular exercise*	2/112
Patients after orthopaedic surgery*	0/10
Acute pulmonary embolism†	0/17
Acute hepatitis	0/22
Angina pectoris	0/25
Acute myocardial infarction	61/64
Myasthenia gravis*	1/21
Progressive muscle dystrophies*	28/28

*Somer *et al.* (1976).
†Konttinen *et al.* (1974).

Results

Heart type creatine kinase isoenzyme (CK MB) was detected in serum in 23 of 53 patients (43%). Its presence was most frequent in cerebral contusion and most rare in ischaemic brain infarction (Table 2). The total creatine kinase (CK) activity was above normal in 26 patients. Five patients showed CK MB activity though their total CK activity was normal. The peak of CK MB activity varied from 3 to 124 U/l (Fig.) and constituted from 1 to 20 per cent of the total CK activity (mean 8·7%).

The presence of CK MB isoenzyme was closely associated with other signs of myocardial injury (Table 3). Electrocardiogram showed signs suggestive of acute myocardial injury in 15 cases: in 13 patients negative transient symmetrical T waves suggestive of subendocardial lesion and in 2 patients pathological Q waves with ST segment changes were generated as an indication of acute transmural infarction. Raised LD_1 was recorded in 11 of these patients. When no CK MB activity was found in serum (in 30 patients) there were electrocardiographic signs suggestive of acute myocardial injury in 2 instances, and LD_1 was increased in 4. The association of serum CK MB activity with electrocardiographic abnormalities ($P < 0{\cdot}001$) as well as raised LD_1 ($P < 0{\cdot}01$) is significant.

Necropsy was performed on 8 patients who had shown serum CK MB activity, and showed subendocardial haemorrhage in 3 cases. In one of them the electrocardiogram gave no hints of acute myocardial injury; in another case no electrocardiogram had been recorded. No acute cardiac lesions were detected in the 3 necropsied patients with no serum CK MB activity.

The patients with CK MB activity in the serum had a higher mortality (14 of 23 patients) than those without serum CK MB activity (7 of 30 patients)

[1]The original method contains an error: the incubation fluid should also contain 40 mg glucose in 5 ml of glycylglycine buffer, in addition to the other reagents mentioned.

Table 2 *Heart type creatine kinase isoenzyme (CK MB), LD_1, electrocardiogram, and necropsy findings in acute cerebral disorders*

	No. of patients	*No. of patients with*			
		Increased serum CK MB	*Increased serum LD_1*	*ECG changes suggestive of acute MI*	*Subendocardial haemorrhage on necropsy*
Ischaemic brain infarction	27	6	4	6	1
Subarachnoid haemorrhage	8	3	4	3	0
Cerebral haemorrhage	4	3	2	3	1
Cerebral contusion	10	9	4	3	1
Bacterial meningitis	4	2	1	2	0
Total	53	23	15	17	3

MI, myocardial injury.

Table 3 *Electrocardiogram, LD_1, and necropsy findings in acute cerebral disorders grouped according heart type creatine kinase isoenzyme (CK MB) in serum*

	CK MB	No. of patients	Frequency of ECG changes suggestive of acute MI	Frequency of increased serum LD_1	Frequency of subendocardial haemorrhage in necropsy
Ischaemic brain infarction	+	6	6/6	2/6	1/2
	-	21	0/21	2/21	0/2
Subarachnoid haemorrhage	+	3	2/3	2/2	0/0
	-	5	1/5	2/4	0/1
Cerebral haemorrhage	+	3	2/3	2/3	1/1
	-	1	1/1	0/1	0/0
Cerebral contusion	+	9	3/5	4/9	1/3
	-	1	0/1	0/1	0/0
Bacterial meningitis	+	2	2/2	1/2	0/2
	-	2	0/2	0/2	0/0
Total	+	23	15/19	11/22	3/8
	-	30	2/30	4/29	0/3

MI, myocardial injury.

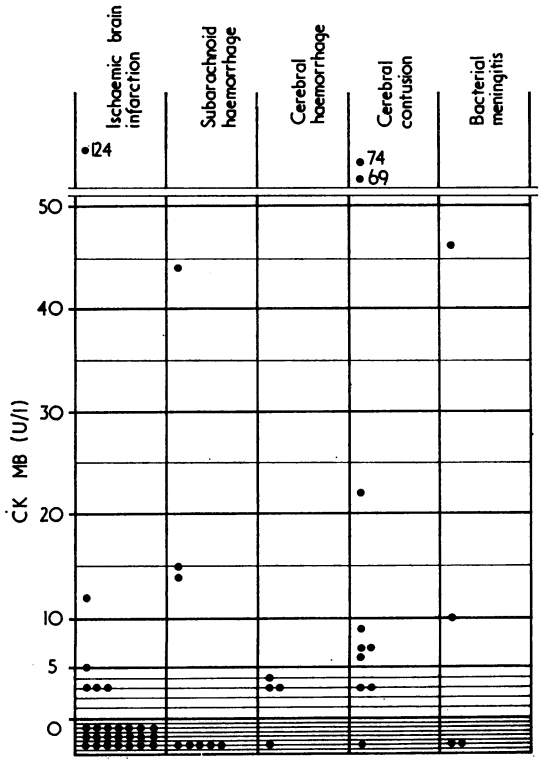

Fig. *Peak values of heart type creatine kinase isoenzyme (CK MB) in patients with acute cerebral disorders. Plots in the hatched area all represent zero CK MB activity.*

(Table 4). The difference is significant ($P < 0.01$). The degree of CK MB isoenzyme increase did not correlate with the mortality nor did the increase of total CK activity.

The patients with electrocardiographic abnormalities suggestive of acute myocardial injury had a higher mortality (11 of 17 patients) than those without such electrocardiographic signs (8 of 32 patients) (Table 5). The difference is significant ($P < 0.01$). The increase of serum LD_1 activity did not correlate with the mortality.

Discussion

Several recent studies have established the value of heart type creatine kinase isoenzyme (CK MB) as a highly heart-specific enzyme test (Konttinen and Somer, 1973; Wagner *et al.*, 1973; Roberts and Sobel, 1976; Smith *et al.*, 1976; Sobel *et al.*, 1976). In addition to myocardial injury, pathological serum CK MB activity may be found in progressive muscle dystrophies. This evidently results from an increased heart type/muscle type isoenzyme ratio in diseased muscle.

Normal skeletal muscle can release excess CK in the serum, but this is muscle type isoenzyme (CK MM), not CK MB (Somer *et al.*, 1976). Brain type creatine kinase isoenzyme (CK BB) is also found in the serum but only transiently in severe acute brain accidents (Kaste *et al.*, 1977).

Our finding of CK MB isoenzyme in the serum in 43 per cent of patients with acute cerebral dis-

Table 4 *Relation between mortality and occurrence of heart type creatine kinase isoenzyme (CK MB) in serum of patients with acute cerebral disorders*

	Mortality of patients with CK MB	*Mortality of patients without CK MB*
Ischaemic brain infarction	4/6	3/21
Subarachnoid haemorrhage	2/3	4/5
Cerebral haemorrhage	3/3	0/1
Cerebral contusion	3/9	0/1
Bacterial meningitis	2/2	0/2
Total	14/23	7/30 $P<0.01$

Table 5 *Relation between mortality and electrocardiographic abnormalities suggestive of acute myocardial injury in acute cerebral disorders*

	Mortality with electrocardiographic abnormalities	*Mortality without electrocardiographic abnormalities*
Ischaemic brain infarction	4/6	3/21
Subarachnoid haemorrhage	2/3	4/5
Cerebral haemorrhage	2/3	1/1
Cerebral contusion	1/3	0/3
Bacterial meningitis	2/2	0/2
Total	11/17	8/32 $P<0.01$

orders strongly suggests myocardial injury as a frequent complication in acute cerebral disorders. This is further supported by the association of serum CK MB activity with other signs indicative of acute myocardial injury such as electrocardiographic abnormalities and increased LD_1 activity in the serum. Furthermore, subendocardial haemorrhage was verified in a few necropsied cases where serum CK MB activity had been present. This had also been suggested by earlier authors, though with less conclusive evidence (Weidler, 1974; Weintraub and McHenry, 1974).

The higher mortality of the patients with CK MB activity in the serum or with electrocardiographic abnormalities suggestive of acute myocardial injury, compared with patients lacking these signs ($P<0.01$), indicates that the prognosis is essentially impaired if acute brain damage is complicated by acute myocardial injury. Though the pathogenesis of heart damage is unknown, the presence of the affection seems to carry considerable weight and to deserve appropriate clinical attention.

This study was supported by the Medical Research Council, Academy of Finland; the Finnish Heart Association; and the Paavo Nurmi Foundation.

References

Kaste, M., Somer, H., and Konttinen, A. (1977). Brain-type creatine kinase isoenzyme. *Archives of Neurology,* **34,** 142–144.

Konttinen, A., Hupli, V., Louhija, A., and Härtel, G. (1969). Origin of elevated serum enzyme activities after direct-current countershock. *New England Journal of Medicine,* **281,** 231–234.

Konttinen, A., and Somer, H. (1973). Specificity of serum creatine kinase isoenzymes in diagnosis of acute myocardial infarction. *British Medical Journal,* **1,** 386–389.

Konttinen, A., Somer, H., and Auvinen, S. (1974). Serum enzymes and isoenzymes. Extrapulmonary sources in acute pulmonary embolism. *Archives of Internal Medicine,* **133,** 243–246.

Roberts, R., and Sobel, B. E. (1976). Elevated plasma MB creatine phosphokinase activity. A specific marker of myocardial infarction in perioperative patients. *Archives of Internal Medicine,* **136,** 421–424.

Roe, C. R., Limbird, L. E., Wagner, G. S., and Nerenberg, S. T. (1972). Combined isoenzyme analysis in the diagnosis of myocardial injury: application of electrophoretic methods for the detection and quantitation of the creatine phosphokinase MB isoenzyme. *Journal of Laboratory and Clinical Medicine,* **80,** 577–590.

Smith, A. F., Radford, D., Wong, C. P., and Oliver, M. F. (1976). Creatine kinase MB isoenzyme studies in diagnosis of myocardial infarction. *British Heart Journal,* **38,** 225–232.

Sobel, B. E., Roberts, R., and Larson, K. B. (1976). Estimation of infarct size from serum MB creatine phosphokinase activity: applications and limitations. *American Journal of Cardiology,* **37,** 474–485.

Somer, H., Dubowitz, V., and Donner, M. (1976). Creatine kinase isoenzymes in neuromuscular diseases. *Journal of the Neurological Sciences,* **29,** 129–136.

Somer, H., Kaste, M., Troupp, H., and Konttinen, A. (1975). Brain creatine kinase in blood after acute brain injury. *Journal of Neurology, Neurosurgery and Psychiatry,* **38,** 572–576.

Somer, H., and Konttinen, A. (1972). Demonstration of serum creatine kinase isoenzymes by fluorescence technique. *Clinica Chimica Acta,* **40,** 133–138.

Wagner, G. S., Roe, C. R., Limbird, L. E., Rosati, R. A., and Wallace, A. G. (1973). The importance of identification of the myocardial-specific isoenzyme of creatine phosphokinase (MB form) in the diagnosis of acute myocardial infarction. *Circulation,* **47,** 263–269.

Weidler, D. J. (1974). Myocardial damage and cardiac arrhythmias after intracranial hemorrhage. A critical review. *Stroke,* **5,** 759–764.

Weintraub, B. M., and McHenry, L. C., Jr. (1974). Cardiac abnormalities in subarachnoid hemorrhage: a resumé. *Stroke,* **5,** 384–392.

Requests for reprints to Dr Markku Kaste, Department of Neurology, University of Helsinki, SF-00290 Helsinki 29, Finland.